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A New Topical Drug Delivery Platform: The Examples of Sildenafil and Ibuprofen.

The rationale for bringing forth a novel topical drug delivery platform for local disorders such as pain, is multifold. Traditional dosage forms, such as oral or intravenous, provide the required therapeutic dose to not only the target site of action, but to the rest of the body as well, often provoking unwanted adverse effects. Local delivery of drugs, such as ibuprofen directly to the site of pain, by means of topical drug delivery may minimize systemic exposure and potentially provide a more rapid onset of relief to achieve a more immediate therapeutic benefit.

Effective technologies for delivering drugs through the skin to treat localized conditions such as pain, sexual dysfunction and other disorders has long been sought (1-3). Successes have been few, and for the most part, were limited to the delivery of uncharged drugs. Most drugs are charged, and it is difficult to have them pass through the *Stratum Corneum (SC)*. However, once the drug permeates the *SC* into the viable epidermis and dermis, the drug more readily diffuses into the deeper tissue to produce a treatment effect at the intended site of action.

The *SC* penetration of uncharged drugs, such as those commonly found in patches, is governed by Fick's first law given in the equation below. J is the steady state flux, C_o is the initial concentration of the drug in the vehicle, D is the diffusion coefficient of the drug through the *SC*, h is the diffusional path length and P is the partition coefficient between the *SC* and the vehicle:

$$\frac{dm}{dt} = J = \frac{D\mathrm{Co}\,P}{h}$$

A drug penetrates the *SC* most readily when it is at the highest thermodynamic activity (*4).* Fick's first law can be rewritten as:

$$\frac{dm}{dt} = \frac{\alpha D}{\gamma h}$$

where α is the thermodynamic activity of the drug in the vehicle (equivalent to PFE in Figure 1 below) and γ is the thermodynamic activity of the drug in the dermal tissue below the *SC (5).* Charged drugs present a convenient opportunity for raising the thermodynamic activity in the vehicle. This was accomplished in this report by formulating the vehicle with substantial concentrations of ionic salts. The ibuprofen cream contains sodium and potassium chloride while the sildenafil cream contains tri-sodium citrate and potassium chloride. The vehicle is a traditional oil and water emulsion comprised of commonly used ingredients. Despite its high ionic strength (~7.5 M in the hydrophilic phase of the cream), the cream is physically and chemically stable at conventional accelerated stability conditions.

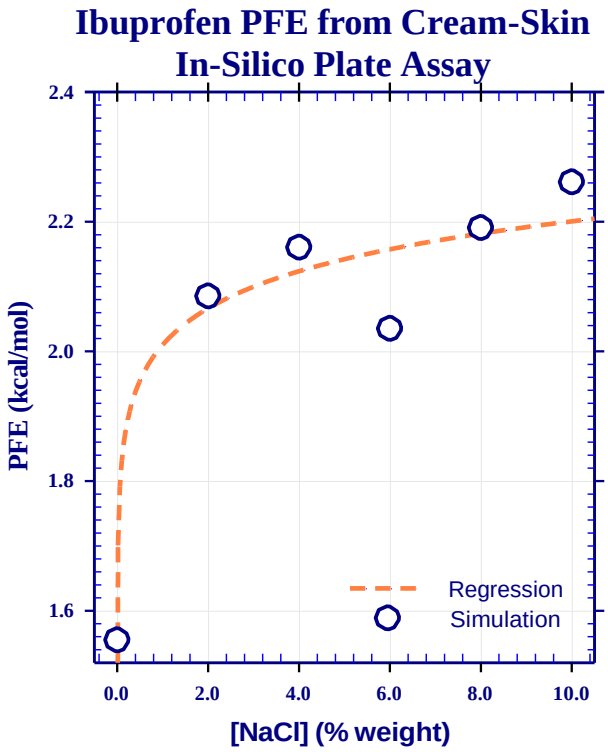

Figure 1. Computer simulation of Partition Free Energy (PFE) of ibuprofen as a function of salt concentration (i.e. NaCl) in a mixture of the cream and stratum corneum (SC) components (e.g., phospholipids, cholesterol, free fatty acids, ceramides). Salt concentration increases PFE to a greater degree when the cream interacts with the SC and deeper tissue.

Of note, it has been shown that drugs which form two or more hydrogen bonds with the *SC* do not readily cross into the viable epidermis and dermis (*6).* The high ionic content in our cream may help prevent this hydrogen bonding from occurring, further facilitating drug delivery into the deeper tissue.

We investigated the cream morphology and the Active Pharmaceutical Ingredient (API) distribution in our high ionic content cream using chemical group computer simulations with the Martini forcefield *(7).*

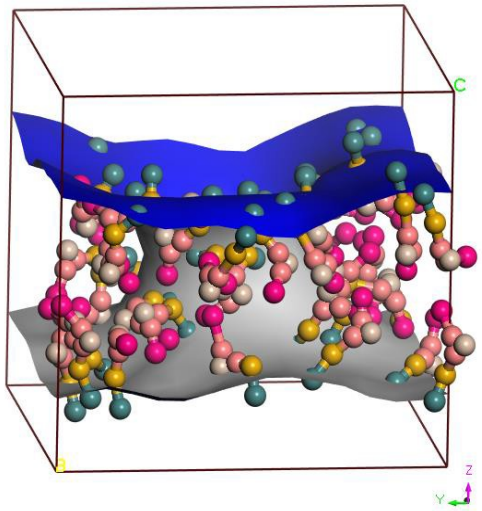

Figure 2. End simulation production run snapshot of cream + sodium ibuprofen. All molecules but the ibuprofen anions are hidden from the display. The hydrophobic/hydrophilic boundary in the cream is depicted by the grey/blue iso-surface, with the blue surface bounding the hydrophilic region. The carboxylic anion chemical group on the ibuprofen molecules is colored in dark green.

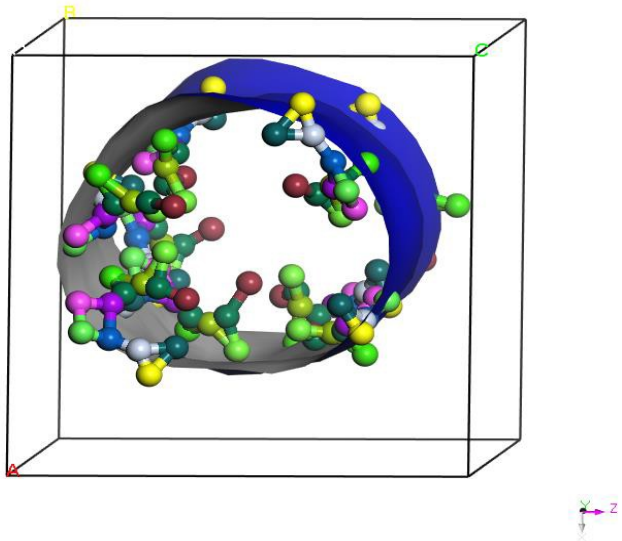

Figure 3. End simulation production run snapshot of cream + sildenafil citrate. All molecules but the sildenafil cations are hidden from the display. The hydrophobic/hydrophilic boundary in the cream is depicted by the grey/blue iso-surface, with the blue surface bounding the hydrophilic region. The protonated group (a nitrogen bonded to the electron donating methyl group in the piperazine ring) on sildenafil is colored in yellow.

The cream displays a largescale morphology of hydrophobic and hydrophilic regions (viz. Fig. 1. and Fig. 2). While the ibuprofen is mostly buried in the hydrophobic domain of the cream (Fig. 1), the carboxylic anionic groups (dark green colored beads) of the ibuprofen molecules reside primarily in the hydrophilic domain of the cream. A similar picture emerges for sildenafil (Fig. 2) where the cationic groups colored in yellow reside primarily in the hydrophilic phase. The ibuprofen molecules are oriented in a rather normal fashion toward the hydrophobic/hydrophilic iso-surface, while the larger sildenafil molecules display a more disordered orientation.

We tested the topical delivery of our ibuprofen cream *in vivo* using the miniature swine (*Sus scrofa*) model. This model has consistently demonstrated to be of substantial value in investigating local and systemic effects of topical formulations. While miniature pig skin is not completely identical to human skin, it is more similar to human skin than that of other laboratory animal models and its value for drug evaluation has been well documented (*8-10*).

Twenty four Sinclair^{TM} Miniature Swine (12 male and 12 female) were randomly assigned to four treatment groups with 3 male and 3 female animals per group. The animals were less than 12 months old and weighed between 25 and 45 kg. The backs (dorsum) of each animal (sourced from Sinclair Research Center, Inc., Auxvasse, MO), were clipped to remove any hair present. The dose application surface area was calculated by an established formula based on animal body weight and was marked as approximately 10% of the total body surface area (*11*). The animals were dosed twice daily at the following dose levels: 0 (vehicle only), 12, 120 and 1200 mg/kg/day for seven consecutive days. The two highest doses, 120 and 1200 mg/kg/day, substantially exceed any anticipated clinical dose. Blood samples were collected and analyzed to determine the ibuprofen concentration on Day 7 at 0, 1, 2, 4, 8 and 24 hours post the last dose.

Topical administration of our ibuprofen cream to Sinclair^{TM} Miniature Swine with twice daily dosing up to 1200 mg/kg/day for seven consecutive days resulted in no treatment-related changes in clinical observation, body weight, feed consumption, clinical pathology, organ weight or gross pathology. At the high dose level mild epidermal/dermal irritation was observed microscopically in three of the six treated animals. No dermal irritation was observed in the low and mid dose level groups.

An analysis of the plasma concentrations (Table 1), determined by liquid chromatography and mass spectroscopy was carried out. The values of maximum plasma concentration (C_{max}), the time of maximum plasma concentration (T_{max}), and the area under the curve (AUC_{last}) were determined by standard methods.

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Table 1.

Dose Level (mg/kg/day)	C_{max} (ng/ml)	T_{max} (hours)	AUC_{last} (h*mg/ml)
12	183	4	2,670
120	2,016	6	30,260
1200	21,861	3	261,110

It is striking that both C_{max} and AUC_{last} are linear and directly dose-proportional over a 100-fold range. The correlation coefficient for AUC_{last} is r=0.99.

In a Phase 1, open-label, within-subject, dose-escalation study the pharmacokinetic (PK) profile and vulvar-vaginal safety of locally applied 5% sildenafil citrate cream was assessed in 21 post-menopausal, healthy women. Three dose levels and a placebo regimen were evaluated: 1 g (0 mg of sildenafil citrate), 1 g (50 mg of sildenafil citrate), 2 g (100 mg of sildenafil citrate), and 4 g (200 mg of sildenafil citrate). Doses were administered sequentially and were separated by a 14-16 day washout period. All 3 dose levels and the placebo were applied both externally to the labia minora and clitoris (approximately 50%) and internally to the vagina (approximately 50%). During each treatment period, a single blood sample was drawn prior to dosing (within 1 hour of the first dose) for a baseline assessment of sildenafil and N-desmethyl metabolite (active metabolite) plasma concentrations. Blood samples were again drawn at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 3, 4, 5, 6, 7, 8, 9, 12, 15, 18, 24, 28 and 32 hours post-dose.

PK results are summarized in Figure 4 below.

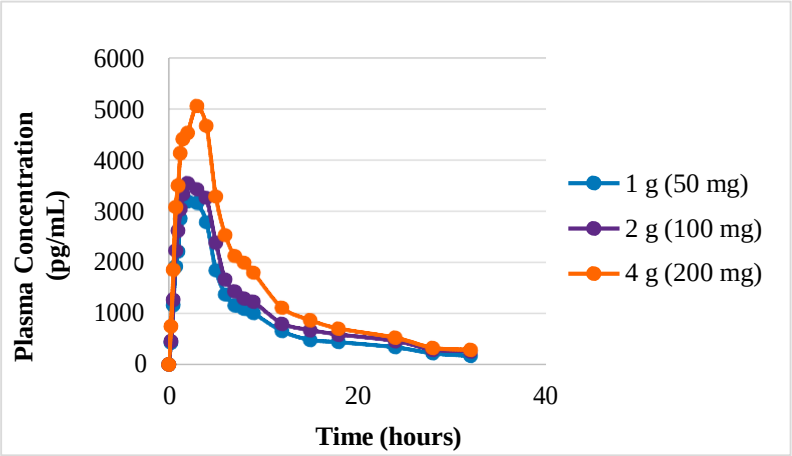

Figure 4. The time course of plasma sildenafil concentration in 21 post-menopausal women following topical administration of 1 g, 2 g, and 4 g of 5% sildenafil citrate cream to the vulvar-vaginal area.

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It is hypothesized that the total amount of sildenafil measured in the blood over 32 hours was initially all concentrated in the vulvar-vaginal tissue. Thus, it is probable that the concentration of sildenafil present in the vulvar-vaginal tissue following application of the proposed clinical dose of 2 g approached or was greater than the drug tissue concentration resulting from a 100 mg oral dose of sildenafil.

The findings presented in this report demonstrate successful implementation of our novel topical drug delivery platform. Increasing thermodynamic activity of ibuprofen and sildenafil in a vehicle cream with high ionic strength effectively delivered drug across the skin in miniature swine and in humans. The cream formulation of ibuprofen referenced in this report is currently in Phase III clinical trials for the treatment of acute pain and the cream formulation of sildenafil citrate used herein is in Phase II clinical trials for the treatment of Female Sexual Arousal Disorder and Erectile Dysfunction in women and men, respectively. This technology is also being applied to several other active pharmaceutical ingredients with localized treatment targets.

References:

1. D.T. Rovee, J.R. Marvel, J.A. Mezick. *US Patent* 4,360,518 (1982)
2. L. Mason, R.A. Moore, J.E. Edwards, S. Derry, H.J. McQuay. *BMC Musculoskelet. Disord.* **5**, 28 (2004)
3. J. Campbell, T. Dunn. *J. Accid. Emerg. Med.* **11**, 178-182 (1994)
4. D.R. Karsa & R.A. Stephenson, *Chemical Aspects of Drug Delivery Systems,* Bradford: Royal Society of Chemistry, p. 43 (1996)
5. H.A.E. Benson. *Current Drug Delivery* **2**, 22-33 (2005)
6. W.J. Pugh, M.S.R. Roberts, J. Hadgraft. *Int. J. Pharma.* **138**, 149-167 (1996)
7. S. J. Marrink, H.J. Resselada, S. Yefimov, D. P. Tieleman and A. H. de Vries, J. Phys. Chem. B. , **111** (27), 7812-7824 (2007)
8. G. Bode, P. Clausing, F. Gervais,J. Loegsted, J. Luft, V. Nogues, J. Sims. *J. Pharmacol. Toxicol. Methods.* **62**, 196-220 (2010).
9. R. Foster, G. Bode, L. Ellegaard, J.W. van der Laan. *J. Pharmacol. Toxicol Methods* **62**, 236-42 (2010)
10. A. Jacobs. *Expert Opin. Drug Metab. Toxicol.* **2**, 345-349 (2006)
11. W. S. Spector. *Handbook of Biological Data* p 175 W. B. Saunders Co., Philadelphia, (1956)

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